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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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☐ *Additional inventors are being named on th____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (280 characters max)

FIXED-DOSE COMBINATION TABLETS

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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☒ Specification *Number of Pages* 35 ☐ CD(s), Number

☒ Drawing(s) *Number of Sheets* 4 ☐ Other (specify)

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C.

P19SMALL/REV05

TITLE OF THE INVENTION

FIXED-DOSE COMBINATION TABLETS

FIELD OF THE INVENTION

The present invention relates to fixed dose combination tablets. The present invention also relates to new oral pharmaceutical compositions for use in the treatment and prophylaxis of gastrointestinal disorders associated with the use of Non Steroidal Anti-Inflammatory Drugs (NSAIDs). More particularly, the present invention relates to pharmaceutical compositions comprising a combination of a non-steroidal anti-inflammatory drug and an H_2-receptor antagonist. Furthermore, the present invention relates to a method for preparing such compositions and to the use of such compositions in medicine.

BACKGROUND OF THE INVENTION

In recent years, interest in multi-layered tablets as oral controlled-release systems, has increased. Multi-layered tablets have some obvious advantages over conventional tablets. They are commonly used to avoid chemical incompatibilities of formulation components by physical separation. Release profiles may be modified by combining layers with different release patterns, *i.e.* by combining slow-release with immediate-release layers.

Conte et al. (1) have proposed an oral controlled-release tablet called Geomatrix®, which is based on the multi-layered tablet concept. Functionally, the product represents a swellable matrix. The swelling of the drug-containing layer causes an increase of the surface area and therefore an increase of the amount of drug released per time interval. At the same time, the outer cover layers control the diffusion of the

drug from the drug containing core. Other examples of orally controlled or modified-release products involving the multiple-layered tablet concept were published by Qiu et al. (2), Yang et al. (3), Abraham et al. (4), Nangia et al. (5), Chidambaram et al. (6).

If the core layer of a multi-layered tablet is completely covered by a surrounding layer, the product is commonly being referred to as a dry-coated tablet. This technique is often used to avoid sugarcoating of a hygroscopic core, but has been replaced to some extent by film-coating techniques. Dry-coating techniques have been suggested to produce scored controlled-release tablets.

Complex multi-layered tablets are multi-layered tablets having differently shaped layers. The shape of the outer layers depends on the shape of the core tablet (Zerbe and Krumme (7)). Cremer and Asmussen (8) and Cremer (US Patent 5,853,760 herein incorporated by reference) first introduced the concept of complex multi-layered tablets to achieve zero-order release from matrix-based systems.

NSAIDs comprise a class of drugs having long been recognized as being of high therapeutic value in the treatment of inflammatory conditions. Despite their therapeutic benefits, the use of NSAIDs is frequently limited by an increased risk of gastrointestinal side-effects such as peptic ulceration and dyspeptic symptoms.

Attempts at modifying the NSAID structure in order to prevent such side-effects have been moderately successful at best. A more promising alternative to the problem of healing and preventing NSAID associated gastrointestinal side-effects, more particularly in patients with a need for continuous NSAID treatment, is to combine the NSAID with an anti-ulcer drug such as for example prostaglandin analogues, H_2-receptor

antagonists such as for example omeprazole or sucralefate, or proton pump inhibitors. Yet another suggested alternative involves the administration of NSAIDs following the ingestion of food or milk.

The NSAID sodium diclofenac has been used for decades for the symptomatic treatment of osteoarthritis and rheumatoid arthritis. Famotidine, an H_2-receptor antagonist, has proven to be useful for the treatment of gastric and duodenal ulcers as well as for the relief of heartburn. Famotidine has also been shown to reduce the frequency of gastric and duodenal ulcers associated with non-selective NSAIDs such as diclofenac, ibuprofen, naproxen, and ketoprofen (*Taha et al.*, New England Journal of Medicine, 1996; 334:1435-1437).

The frequency of gastric and duodenal ulcers associated with COX-2 inhibitors and non-selective NSAIDs in patients suffering from osteoarthritis and rheumatoid arthritis, as well as in a subset of these patients additionally taking low dosages of aspirin, has also been investigated. Commercially available COX-2 inhibitors such as Celebrex®, Viox® and Bextra® have been shown to produce a lower frequency of gastroduodenal ulcers than non-selective NSAIDs. However, low dosages of aspirin administered with COX-2 inhibitors, substantially increases the frequency of upper GI ulceration. This seems to indicate that COX-2 inhibitors do not offer sufficient protection against ulcers induced by low-dosages of aspirin, which in turn has important implications since a large portion of patients suffering from osteoarthritis and rheumatoid arthritis also ingest low dosages of aspirin.

Few examples regarding NSAID pharmaceutical formulations are known in the prior art.

US Patent 5,601,843 issued on February 11, 1997 to *Gimet et al.* describes pharmaceutical compositions, more specifically a core/mantle tablet, comprising a core consisting of an NSAID, which is either diclofenac or piroxicam, and a coating incorporating a prostaglandin such as misoprostol. Misoprostol, even though it effectively prevents NSAID-induced gastroduodenal ulceration, is associated with a high incidence of adverse effects such as abdominal pain, diarrhea, nausea and flatulence.

US Patent 6,287,600 issued on September 11, 2001 to *Quali et al.* describes pharmaceutical compositions for oral administration consisting of a bi-layer tablet, comprising an NSAID and a prostaglandin, and wherein the NSAID is enterically coated.

US Patent 6,387,410 issued on May 14, 2002 to *Woolfe at al.* discloses oral pharmaceutical dosages, more specifically multi-layer tablets, comprising a mixture of a delayed release formulation of an NSAID and a mixture comprising a prostaglandin, wherein the NSAID formulation is in the form of beads or granules that are coated to provide programmed release according to the position in the gastrointestinal tract.

US Patent 6,372,255 issued on April 16, 2002 to *Saslawski et al.* describes multi-layer tablets for the instant and then prolonged release of active substances. The tablet comprises a first layer containing an active substance in the form of a granule, and which disintegrates immediately upon contact with an aqueous medium such as a physiological medium. Furthermore, the tablet comprises a second layer which is composed of an inert matrix in which is dispersed a second active substance allowing for a prolonged release of the active ingredient.

US Patent 6,365,184 issued on April 2, 2002 *to Depui et al.* teaches multiple unit fixed dosage oral formulations comprising an NSAID (diclofenac) and an acid susceptible proton pump inhibitor (omeprazole). The proton pump inhibitor is generally in the form of enterically coated pellets capable of compression into tablets together with the NSAID. The enteric coating layer has mechanical properties such that the acid resistance of the enterically coated pellets is not significantly affected by the compression of the pellets with the other components during tableting.

There thus remains a need to develop an improved fixed-dose combination tablet containing an extended-release NSAID and an H_2-receptor antagonist for the treatment of osteoarthritis in patients also taking low dosages of aspirin.

The present invention seeks to meet these and other needs.

The present invention refers to a number of documents, the content of which is herein incorporated by reference in their entirety.

SUMMARY OF THE INVENTION

The present invention relates to a novel fixed dose multi-layer tablet comprising two or more drug combinations, as well as to methods of making the multi-layer tablet.

The present invention relates to an improved fixed-dose multi-layer tablet containing an extended-release NSAID and an H_2-receptor antagonist, useful for the treatment of osteoarthritis in patients who are susceptible to developing NSAID-induced gastric and duodenal

ulcers, and who are also taking low doses of aspirin for the prevention of myocardial infarction.

The present invention relates to an improved fixed-dose pharmaceutical formulation containing an extended-release NSAID and an H_2-receptor antagonist, wherein a first portion of the H_2-receptor antagonist is released following an immediate release profile and wherein a second portion is released following an extended release profile.

The present invention also relates to a method for reducing the undesirable gastrointestinal side effects associated with the oral administration of NSAIDs, comprising administering a fixed-dose multi-layer tablet containing an NSAID and an H_2-receptor antagonist to a patient in need thereof.

In one embodiment, the present invention relates to an improved fixed dose oral multi-layer tablet comprising diclofenac and famotidine.

In another embodiment, the present invention relates to a method for treating or preventing osteoarthritis in patients susceptible to developing NSAID induced gastric and duodenal ulcers, comprising administering an effective amount of a fixed-dose multi-layer tablet containing an NSAID and an H_2-receptor antagonist.

In yet another embodiment, the present invention relates to a method for treating or preventing osteoarthritis in patients susceptible to developing NSAID induced gastric and duodenal ulcers, and who are also taking low doses of aspirin for the prevention of myocardial infarction, comprising administering an effective amount of a fixed-dose multi-layer tablet containing an NSAID and an H_2-receptor antagonist.

Further scope and applicability will become apparent from the detailed description given hereinafter. It should be understood however, that this detailed description, while indicating preferred embodiments of the invention, is given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a multi-layered dosage form comprising an immediate release layer (IR) comprising X mg of drug A, a sustained release (SR) layer comprising Y mg of drug A as well as a sustained release core comprising Z mg of drug B.

Figure 2 shows an *in-vitro* dissolution profile for immediate release (IR) and sustained release (SR) layers containing drug A, obtained in SGF at 100 rpm and 37°C.

Figure 3 shows an *in vitro* dissolution profile for a sustained release (SR) core comprising drug B.

Figure 4 shows *in vitro* dissolution profiles, obtained simultaneously from a multi-layer tablet containing drug A, subdivided in immediate and sustained release layers, and drug B, present in a sustained release core.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the terms "active agent", "active ingredient", "drug" and "pharmaceutically active agent" are used interchangeably to refer to a compound which, when administered to an organism (human or animal) induces a desired pharmacological effect.

As used herein, the term "effective amount" or "therapeutically effective amount" is well known in the art. It is meant to describe a non-toxic but sufficient amount of the agent to provide the desired therapeutic effect. An appropriate "effective amount" in any individual case may be determined by one of ordinary skill in the art using only routine experimentation.

The pathogenesis of NSAID-induced gastroduodenal mucosal injury encompasses topical injury as well as systemic mechanisms. Topical mucosal injury is believed to be mediated by the inherent acidic properties of aspirin as well as many other NSAIDs. Systemic effects are thought to be largely the result of the inhibition of endogenous prostaglandin synthesis.

Pharmaceutical formulations wherein an NSAID such as for example diclofenac is combined with an H_2-receptor antagonist, such as for example famotidine, will help and prevent NSAID-induced ulcers in patients suffering from osteoarthritis and rheumatoid arthritis in addition to preventing aspirin induced ulceration.

The present invention relates to improved fixed-dose pharmaceutical compositions comprising a non-steroidal anti-inflammatory drug and an H_2-receptor antagonist, capable of addressing both topical and systemic mechanisms. In a broad sense, the present invention relates to improved, fixed-dose pharmaceutical compositions, comprising a non-steroidal anti-inflammatory drug and an H_2-receptor antagonist. More specifically, the present invention relates to an improved fixed-dose combination tablet capable of immediately releasing a first portion of an H_2-receptor antagonist in the gastroduodenal lumen, followed by concomitantly releasing a second sustained release portion (extended release profile) with a sustained release NSAID. The immediate release

portion of the H_2-receptor antagonist addresses any possible topical ulcerogenic effects, whereas the sustained portion addresses any systemic ulcerogenic effects of the NSAID. In one particular embodiment of the present invention, diclofenac is used in combination with famotidine. The multi-layered tablet is preferably prepared by first producing the NSAID containing core (in the form of a layer structure), followed by at least partially coating it with an erodable layer comprising a first portion of the H_2-receptor antagonist, providing for a sustained release of the antagonist. A third, immediate release layer containing a second portion of the H_2-receptor antagonist, is then applied.

Diclofenac is an NSAID having acidic properties. The design of sustained release formulations comprising drugs having acidic properties, constitutes an important problem. The low pH environment commonly encountered in the stomach suppresses the ionization of acidic drugs thus considerably reducing the solubility of these drugs in gastric juices. A pH increase, as is observed in the intestines, results in a solubility increase and a faster release rate. The fixed dose formulations of the present invention provide for constant plasma levels of acidic drugs, such as sodium diclofenac, throughout the digestive tract.

Famotidine's primary pharmacological function is the inhibition of gastric secretion. Famotidine was shown to inhibit basal and nocturnal gastric secretion, as well as food and pentagastrin stimulated secretion, one hour following oral administration. The maximum effect is dose dependent, and was observed within one to three hours following oral administration. Doses of 20 mg and 40 mg effectively inhibit gastric secretion over periods ranging from 10 to 12 hours. The nocturnal intra-gastric pH was raised to mean values of 5.0 and 6.4 following nocturnal doses of 20 mg and 40 mg respectively. The basal daytime inter-digestive

pH, at three and eight hours following the administration, after breakfast, of 20 or 40 mg of famotidine, was raised to about 5 (Physician's Desk Reference, 2000).

The combination of an H_2-receptor antagonist with an NSAID in a sustained release dosage form, provides for better patient compliance and increased efficiency of the NSAID. The suppression of gastric secretion by the H_2-receptor antagonist significantly reduces the rate of occurance of ulceration, in addition to increasing the intra-gastric pH, which favorably effects the solubility and absorbance of the NSAID. The present fixed dose pharmaceutical compositions provide for an immediate release of a first portion of an H_2-receptor antagonist, followed by the concomitant controlled release of an NSAID with a second portion of the H_2-receptor antagonist.

Tablet design

The pharmaceutical compositions of the present invention are multi-layered solid fixed-dosage forms. The compositions can be administered once-daily or twice-daily, depending on the dosage of the active components. Both dosage forms will provide for sufficient plasma levels for the treatment of osteoarthritis, while at the same time preventing the formulation of NSAID induced gastric ulcers. This is of particular benefit to patients also taking low dosages of aspirin as a preventive measure against myocardial infarction. The H_2-receptor antagonist is released following two distinct release profiles; a first portion being released following an immediate release profile and a second portion being released following an extended release profile.

In order to achieve the controlled release of pharmacological agents, several systems were investigated: diffusion systems, erodable systems and osmotic systems.

Diffusion systems include reservoir devices, wherein a drug containing core is covered by a polymeric membrane. A matrix devices is another example of a fusion system wherein a dissolved or dispersed drug is distributed uniformly throughout an inert polymeric matrix. In the case of reservoir devices, the drug is released by flowing through the membrane, which flow can be described by a Fick's first law of diffusion. In the case of matrix systems however, the mechanism of drug release first involves dissolution of the drug from the surface layer followed by dissolution from the underlying layer and fusion through the overlying drug depleted layer.

Erodable systems are based on the inherent dissolution rate of the drug itself. The dissolution rate can be influenced by coating the drug with a slow dissolving coat or by incorporating the drug into a slowly dissolving carrier.

Osmotic systems are generally tablets consisting of a drug containing core which is coated by a semi-permeable membrane having a small orifice. Exposure of the tablet to gastric fluids causes water to enter the tablet through the membrane while pumping the drug out through the orifice at a constant rate.

In practice, controlled release of an active compound can be achieved by more than one mechanism. From the same pharmaceutical dosage form, drug release can occur for example by simultaneous swelling and diffusion, simultaneous diffusion and erosion, and simultaneous swelling, diffusion and erosion.

In the case of matrix systems, the rate of drug release is largely dependant on the properties of the composition used to make the matrix, as well as physical properties and concentration of the active and the geometry of the matrix. Tablet diameter and surface area of the tablet are additional factors influencing the amount of drug release.

Multi-layer tablets represent a new approach based on the active surface area available for drug release. Multi-layer tablets consist of a core comprising an active containing matrix and one or more barriers (external layers) capable of delaying the interaction between the core content and the dissolution medium limiting the solvent penetration rate.

Varying the geometry of the layers, or using layers characterized by specific release properties, allows for the modulation of the release profile of a drug.

The tablets of the present invention useful for the treatment of osteoarthritis comprise a pharmaceutical formulation containing two active ingredients (Figure 1). The first active ingredient is an H_2-blocker antagonist, divided into two portions. A first portion is formulated in an immediate release (IR) layer and a second portion is formulated in a sustained release layer (SR). The immediate release layer based on a fast disintegration process, will preferably contain between 5 to 25% of the H_2-receptor antagonist. The pharmaceutical (H_2-receptor antagonist) formulation of this layer consists mainly of a dry mixture of active and pharmaceutically acceptable excipients such as for example cellulose derivatives, sugar, soluble salts, and other excipients well known by a person skilled in the art. Additives such as colorants, fillers anti-tacking and antistatic agent such as for example magnesium stearate and talc may also be incorporated into the formulation.

The sustained release layer will preferably contain between 75 to 95% of the H_2-receptor antagonist. The antagonist may be directly mixed with pharmaceutically acceptable excipients or it may be first coated with hydrophilic or hydrophobic agents, which are specifically chosen to regulate the rate of release of the antagonist. The sustained release layer may further comprise polymeric materials which are slowly water-soluble and/or slowly gel forming when exposed to an aqueous medium such as cellulose derivatives and modified starches. The sustained release layer is then applied to an NSAID containing core. The thickness of the sustained release layer can be varied, depending on the specific requirements. It's main role resides in limiting and adjusting the release of the NSAID contained in the core, as well sustaining the release of the H_2 receptor antagonist. This objective can be achieved by incorporating an erodable mass of solids into the sustained release layer. Another option is to design a formulation allowing for the diffusion of the H_2 receptor antagonist from a relatively stable sustained release layer and which simultaneously limit the release of the NSAID from the core.

Matrix forming excipients are commonly used to ensure a sustained release of pharmaceutical active compounds. Such materials form a hydrophilic / hydrophobic matrix allowing for the sustained release of the active following both diffusion and erosion mechanisms. Hydrophilic drugs are predominantly released via diffusion through the matrix. Depending on the polymer selected, a combination of diffusion and erosion mechanisms control the rate of drug release. The term "erosion" is generally accepted in the pharmaceutical arts as being a process in which solid masses are cleared away. Surface area fluctuation plays an important role in those cases where erosion is the leading factor in controlling the rate of drug release. An erodable mass is commonly generated by

polymers including polysaccharides, polylactides, polyglycolides, polyethylenes and polypropylenes, polyvinyl alcohol, polyvinyl acetates, polyvinyl chlorides and polyvinyl pyrolidones.

The second active ingredient is an NSAID, which is formulated into a separate sustained release layer, more specifically the core of the multi-layer tablet. The sustained release core will preferably contain between 50 to 100% of the recommended daily dose of the NSAID, and is prepared in accordance with known techniques in the art. The core composition represents an easily flowable homogeneous mixture that is compressed under a pressure ranging between 3 and 10 kN.

Insoluble polymers such as cellulosic materials, polyvinyl acetates, polyvinyl alcohols, methacrylates and non-crosslinked polyvinylpyrolidone are used in the core formulations, in addition to adjuvants such as for example sucrose, lactose, colloidal silica and magnesium stearate. The ratio of polymer to active in the core formulation varies with the type of active ingredient.

Multi-layered tablets possess numerous advantages when compared to conventional dosage forms. Chemically incompatible components can be incorporated into a multi-layered tablet by integrating them into separate layers. Furthermore, a different active component can be incorporated into the distinct layers of a multi-layered tablet, thereby offering the possibility of designing each layer so as to obtain a desired release profile for each active and thus maximizing both their individual and combined therapeutic effect.

The tablets may be designed to have pulsatile, delayed onset or any suitable predetermined release profile. In one embodiment, this is achieved by designing a multi-layered tablet. The

different layers of the multi-layered tablet may comprise different active agents, different amounts of active agent and/or different forms of active agent. The different layers of the multi-layered tablet may also comprise different proportions of a polymer and different kinds of other pharmaceutical excipients, thus providing for additional control of the release of the active agents from the tablet. As the multi-layered tablet is slowly dissolving as it passes through the digestive tract, it releases varying amounts of active agent (or different active agents) at different times, i.e., in different anatomical compartments (e.g., small intestine versus colon). This effectively allows for the design of a programmable active agent release scheme. For example, it may be desirable to initially release larger amounts of the active agent (to be absorbed, *e.g.*, in the stomach or upper end of the small intestine), while gradually releasing diminishing amounts of the active agent as the tablet passes through to the end of the colon (or vice versa). Alternatively, it may be desirable that two active agents be released, or that one active agent is released in the upper digestive tract (e.g., stomach or small intestine) while another active agent is released in the lower digestive tract.

Active components having different water solubilities, requiring different dosages, and having different absorption profiles, can be formulated into a multi-layered tablet. A biphasic controlled release delivery system, allows for the combination of two active components in such a way that the bioavailability is essentially similar to that of a separate administration of each active. A suitable ratio of the two active ingredients into a single dosage form, provides many important advantages from a therapeutic perspective.

A drug released by diffusion from a core displays a Fickian release profile. However, when the core is covered with erodable

layers, the controlled erosion of these outer layers results in a steady increase of the surface area available for the release of the drug, thus providing a linear drug release.

The NSAID, such as diclofenac, is present in the composition in a therapeutically effective amount; preferably the composition is in unit dosage form. When used, diclofenac will be present in the composition in the range of approximately 50 to about 150 mg, and more preferably in an amount of about 75 mg.

The active agents of the present composition, i.e., both the NSAID and the H_2-blocker, may be administered in the form of a pharmaceutically acceptable salt, ester, amide, prodrug or analog or as a combination thereof. Salts, esters, amides, prodrugs and analogs of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example by J. March in "*Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*", 4th Edition (John Wiley & Sons, New York, 1992).

It is to be understood that the present invention is not to be limited to fixed dose combination tablets comprising an NSAID such as diclofenac, and an H_2-receptor antagonist such as famotidine. Other non-limiting examples comprise ibuprofen / famotidine; aspirin / famotidine; morphine / diclofenac; pioglitazone / metformin; ACE-I / statin; and ACE-I / β-blocker.

In a preferred embodiment of the invention, the potential for gastric erosion is reduced by ensuring that a sufficient amount of the H_2-blocker, such as famotidine is released before the release of diclofenac. The immediate release of the H_2-blocker helps raise the pH of

the gastric fluid, which in turn aids in the dissolution of the NSAID such as diclofenac.

Examples

Example 1: Formulation of an immediate release layer, containing drug A.

The immediate release layer contains from about 10 to about 30% of the H_2 receptor antagonist, homogeneously mixed with a disintegrant, in a ratio ranging from about 1:10 to about 2:8.

A 100 mg layer containing 10% of drug A and microcrystalline cellulose (Avicel PH 102 grade, Dow Chemical). The bulk drug was sieved prior to use, and dry-mixed with the polymer. The compression was performed in a Korch EK 0 tableting machine using a round die (diameter 10.0 mm). The final compression force should be between 10 and 20 kN.

Example 2: Formulation of a sustained release layer, containing drug A.

The sustained release layer containing drug A needs to exhibit narrowly defined erosive properties and, at the same time, maintain good bonding to the core. The erosion rate of the core-covering layer, has to be adjusted to match the intended duration of drug A release and to provide the required continuous increase of surface area of the core over the same duration of the application.

An erodable layer can typically be manufacture as follows:

Dry blending a mixture comprising from about 5 to about 40% of active, from about 5% to about 50% of a hydrophilic polymer and from about 5% to about 50% of a hydrophobic polymer, and less then about 2% of a lubricant (magnesium stearate); compressing the composition in a hydraulic press, together with a pre-compressed core containing drug B.

In one preferred embodiment, part of drug A was also formulated as a SR layer which contained between 15 to 80% of the

combined amount of A. An erodable layer weighing about 150 mg, comprises about 30% hydroxypropylmethyl cellulose (Methocel K100), 20% ethyl cellulose (Ethocel EC-20™), lactose and lubricant (1%). The mixture was compressed in a Korch EK0 tableting machine, using a round die (diameter of 10.0 mm), at a compression force of about 10 KN.

In vitro dissolution tests in aqueous solution at different pH values were conducted with tablets based on the formulations of Examples 1 and 2, using Apparatus II and the method detailed in USP 25. The stirrer paddle speed of the apparatus was 100 rpm, and the temperature of the medium was maintained at 37 °C. The dissolution was observed at two pH values: pH 1 (in simulated gastric fluid - SGF) and pH 6.8 (simulated intestinal fluid - SIF). Aliquot samples were assayed for drug A by UV spectrophotometric measurements and the test results are shown in Figure 2.

Example 3: Preparation of a SR core containing drug B

The sustained release matrix containing the NSAID is preferably provided as a plastic core made in accordance with the following steps:

a) intimately blending a pharmaceutically acceptable salt of drug B (about 10-40% by weight) with about 5-30% ethylcellulose (preferably EC-22, Aqualon) and a channeling agent preferably lactose monohydrate (about 25-70%) in a planetary or high shear mixer;

b) Adding to the homogeneous blend from step (a), a solution of ethylcellulose (with about or less then 10% polymer in ethanol) and monitoring the granulation process in order to obtain a uniform and complete distribution of the granulation liquid in the powder blend.

The release properties of the drug from the core are dependent on the ratio of soluble to insoluble components, their particle sizes, the level of compaction, and the remaining porosity of the system. In addition to the physicochemical properties of the powder materials, the homogeneity of the blend and the distribution of the binders within the mix are essential. Consequently, processing conditions selected for the granulation process determine the porosity of the granules and, eventually, the compression parameters of the final tablet. Throughout the process, the viscosity, the particle structure (consistency), the mixer speed and the chopper speed are parameters that are constantly monitored.

c) drying the wet granules at about 50-60°C;

d) size reducing of dried granules in a mill (preferably a Hammer mill) to obtain a granule size less than 2000 microns;

e) homogeneously blending the milled granules with a flowing agent such as silicone dioxide (less than 4%) in a blender (Inversina);

f) dry blending the mixture with a lubricant such as magnesium stearate (about or less than 3%)

g) compressing the composition under a force ranging from between about 3 kN to about 10 kN.

The plastic core could also be obtained by the direct compression method using Drug B 25-45% polyvinyl acetate and polyvinyl pyrolidone blends (approx 20-60%), silicone dioxide (1-3%) and Magnesium stearate (less then 3%).

SR formulations for a 200 mg core comprising drug B were prepared using various drug B / polymer ratios (*i.e.* 1:1, 1:1.5 and 1:2). A dry-mixture of powders was passed through a 30 mesh screen and

extra glidands and lubricants were added in a proportion of about 1% for each excipient, relative to the total core weight

The mixture was compressed at a compression force of about. 10 KN in a Korch EK 0 tableting machine having a round die diameter of 9.8 mm. The influence of the compression force on the mechanical properties of the core, on the interlayer binding as well as on the *in vitro* dissolution profiles was studied. It was found that varying degrees of core hardness do not affect the dissolution of the drug in an aqueous medium. However, a very high compression force could induce weak interlayer binding. Figure 3 illustrates a release profile of drug B in SIF medium.

Example 4: Manufacture of a multi-layer tablet.

Using multi-layer technology, one active (drug B) was compressed in a SR core The core was then transferred into a rotary press, followed by the addition of the other two blends (IR and SR preparations of drug A). In such a way a three-layer tablet can be independently processed using wet or dry granulated materials, as needed to enhance flow or compressibility.

General Procedures

There are three general methods for preparing the materials to be included in the solid dosage form prior to compression: (1) dry granulation; (2) direct compression; and (3) wet granulation.

Dry granulation procedures may be utilized where one of the constituents, either the drug or the diluent, has insufficient cohesive or flow properties to be tabletted. The method includes mixing the ingredients, slugging the ingredients, dry screening, lubricating and finally compressing the ingredients.

Direct compression, involves directly compressing the powdered material(s) to be included in the solid dosage form without modifying the physical nature of the material itself.

An active agent can be pelletized or granulated using any suitable method known in the art. Pelletization or granulation is commonly defined as a size-enlargement process in which small particles are gathered into larger, permanent aggregates in which the original particles can still be identified. Prior to granulation, a binder can be added to the active agent to improve the granulation process.

Solvents and binders are typically added to a formulation to provide larger aggregates of granules. The temperature during granulation is generally not exceeding the melting point of any of the components of the formulation. Typically, the mixture is granulated at a temperature ranging from about 35°C to about 65°C for a period ranging from about 20 to 90 minutes. The granules are then typically air dried for a suitable duration (e.g. one or more hours).

Preferably, the active agents are granulated using high shear mixer granulation or fluid-bed granulation. Both of these

granulation processes provide enlarged granules or pellets, but differ in the apparatus. In high shear mixing, blending and wet massing is accomplished by high mechanical agitation using an impeller and a chopper.

Fluidization is an operation by which fine solids are transformed into a fluid-like state through contact with a gas. At certain gas velocities, the fluid will support the particles, giving them freedom of mobility without entrainment. Such a fluidized bed resembles a vigorously boiling fluid, with solid particles undergoing extremely turbulent motion, which increases with gas velocity. Fluidized bed granulation is therefore a process by which granules are produced in a fluidized bed by spraying a binder solution onto a fluidized powder bed to form larger granules. The binder solution can be sprayed from, *e.g.*, a spray gun positioned in any suitable manner (*e.g.*, top or bottom). The spray position and the rate of spraying may depend on the nature of the active agent and the binder used, and can be readily determined by those skilled in the art.

Optionally, granulated active agents can be milled. The mesh size for the screen can be selected depending on the size of the active agent granule or pellet desired. Typically, the mesh size can range from about mesh 20 to about mesh 100. The milling process aids in providing relatively uniform active agent granules. After the granulated active agents are milled, they may be further dried (*e.g.*, in the air) if desired.

Typically, the mean size of the active agent granule or pellet can range from about 50 μm to about 3 mm, optionally from about 100 μm to about 2 mm, or from about 300 μm to about 1 mm.

The bulk density or the tap density of the active agent granules or pellets ranges from about 0.1 g/ml to about 1.5 g/ml, optionally from about 0.3 g/ml to about 0.8 g/ml, or from about 0.4 g/ml to about 0.6 g/ml. The bulk density is measured based on the USP method.

Compression into tablets

Tabletting form can be accomplished using a tablet press. The tablet is formed by applying pressure on the lower and upper punches. Typical compression pressures range from about 6 kN to about 36 kN and will vary based on the desired size and hardness of the tablet. Preferably the compression pressure is adjusted depending on the formulation characteristics and on the interlayer binding. A strong bond between cover layers and the core matrix layer is mandatory to ensure an erosion-controlled linear release of the drug from the core matrix. Obviously, the physicochemical properties of the formulations are important factors influencing the layer bonding as are the surface roughness and the hardness of the core, and hence its susceptibility to further compression. The pre-compression force is therefore an essential parameter. If the compaction of the core granules exceeds a certain range, a tightly packed, "closed" surface of the core is formed. In such a tightly packed core, no penetration of particles of the cover layer into the core layer will occur during the main compression, which is essential for the formation of a strong bond between the two layers.

Materials

One or more binders may be present in addition to, or in lieu of, the fillers in an amount ranging from about 0 to about 35%, and preferably from about 0.5 to about 30% by weight of the composition. Non-limiting examples of such binders, suitable for use herein, include

polymeric materials (from natural or synthetic source), sugars, as well as a wax binder such as carnauba wax, paraffin, spermaceti, or microcrystalline wax.

The polymeric material is a member selected from the group consisting of chitosan, modified starches, zein, maltodextrin, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, cellulose acetate membrane, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyacrylic acid, metacrylate copolymers, polyvinyl acetate, poly(vinylacetate phthalate), poly(vinyl alcohol), polyethylene oxide, polyethylene glycol, poly(vinyl pyrrolidone), poly(lactic acid), poly(glycolic acid), poly(lactic/glycolic acid), poly(dimethyl silicone), poly(hydroxyethyl methacrylate), poly(ethylene/vinyl acetate), poly(ethylene/vinyl alcohol), or a mixture thereof.

The composition being in the form of a tablet, will include one or more tableting lubricants in an amount ranging from about 0.2 to about 8% and preferably from about 0.5 to about 2% by weight of the composition. Non-limiting examples of such lubricants are magnesium stearate, stearic acid, palmitic acid, calcium stearate, talc, carnauba wax and the like. Other conventional ingredients, which may optionally be present, include preservatives, stabilizers, anti-adherents or silica flow conditioners or glidants, such as silicon dioxide.

If so-desired, the multi-layer tablets of the present invention may include appropriate amounts of other pharmaceutically acceptable excipients such as vehicles (*e.g.*, lactose, mannitol, potato starch, wheat starch, rice starch, corn starch, and crystalline cellulose), binders (*e.g.*, hydroxypropylmethylcellulose, hydroxypropylcellulose,

methylcellulose, and gum arabic), swelling agents (*e.g.*, carboxymethylcellulose and carboxymethylcellulose calcium), lubricants (*e.g.*, stearic acid, calcium stearate, magnesium stearate, talc, calcium hydrogen phosphate, and anhydrous calcium hydrogen phosphate), fluidizers (*e.g.*, hydrous silica, light anhydrous silicic acid), colorants (*e.g.*, red iron oxide), surfactants (*e.g.*, sodium lauryl sulfate, sucrose fatty acid ester), coating agents.

The pharmaceutical compositions of the present invention may further comprise a disintegrant. Disintegrants are agents that aid in the disintegration of the tablets and include, but are not limited to, starch, clays, microcrystalline cellulose, sodium starch glycolate, and cross-linked polymers, preferably, crospovidone. The amounts of each excipient used can be readily determined by routine experimentation.

The tablets of the present invention may further comprise a coating - a light protective layer that may account for about 0 to about 15% by weight of the tablet composition. The coating layer which is applied over the entire tablet may comprise any conventional coating formulations and will include one or more film-formers or binders, such as a hydrophilic polymer like hydroxypropylmethylcellulose, and/or a hydrophobic polymer like methacrylic acid esters neutral polymer, ethyl cellulose, cellulose acetate, and one or more plasticizers, such as triethyl citrate, diethyl phthalate, propylene glycol, glycerin, butyl phthalate, castor oil and the like.

The film formers are applied from a solvent system containing one or more solvents including water, alcohols such as ethyl alcohol or isopropyl alcohol, ketones like acetone, or ethylmethyl ketone, chlorinated hydrocarbons like methylene chloride, and dichloroethane.

Where a color is employed, the color will be applied together with the film former, plasticizer and solvent compositions.

Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified without departing from the spirit and nature of the subject invention as defined in the appended claims.

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CLAIMS

1. A pharmaceutical tablet composition comprising:

(a) a matrix containing core having a pharmaceutically effective amount of a first drug;

(b) a second layer covering said matrix containing core and having a first portion of a second drug and/or an additional amount of said first drug;

(c) a third or more layers having a second portion of said second drug, and/or additional drugs.

2. A pharmaceutical tablet composition comprising:

(a) a matrix containing core having a therapeutically effective amount of a first drug;

(b) a sustained release layer covering said matrix containing core and having a first portion of a second drug; and

(c) an immediate release layer covering said sustained release layer and having a second portion of said second drug,

wherein said sustained and said immediate release layer together provide a therapeutically effective amount of said second drug.

3. A pharmaceutical tablet composition as defined in claims 1 and 2 wherein said matrix containing core further comprises insoluble polymers and adjuvants.

4. A pharmaceutical tablet composition as defined in claim 3, wherein said insoluble polymers are selected from the

group consisting of cellulosic materials, polyvinyl acetates, polyvinyl alcohols, methacrylates, and non-crosslinked polyvinylpyrolidone.

5. A pharmaceutical tablet composition as defined in claim 3, wherein said adjuvants are selected from the group consisting of sucrose, lactose, colloidal silica, and magnesium stearate.

6. A pharmaceutically tablet composition as defined in claim 2, wherein said sustained release layer further comprises water-soluble and/or gel forming polymeric materials.

7. A pharmaceutical tablet composition as defined in claim 2, wherein said immediate release layer further comprises pharmaceutically acceptable excipients selected from the group consisting of cellulose derivatives, sugar, soluble salts, colorants, fillers, anti-tacking agents and anti-static agents.

8. A pharmaceutically tablet composition as defined in claim 6, wherein said sustained release layer comprises from about 75 to about 95% of said second drug.

9. A pharmaceutical tablet composition as defined in claim 7, wherein said immediate release layer comprises from about 5 to about 25% of said second drug.

10. A pharmaceutical tablet composition as defined in claims 1 and 2, wherein said first drug is an NSAID.

11. A pharmaceutical tablet composition as defined in claim 10, wherein said NSAID comprises diclofenac.

12. A pharmaceutical tablet composition as defined in claim 11, comprising from about 50 to about 150 mg of diclofenac, more preferably about 75 mg of diclofenac.

13. A pharmaceutical tablet composition as defined in claims 1 and 2, wherein said second drug is an H_2-receptor antagonist.

14. A pharmaceutical tablet composition as defined in claim 13, wherein said H_2-receptor antagonist is famotidine.

15. A pharmaceutical tablet composition as defined in claim 14, comprising from about 20 to about 60 mg of famotidine, more preferably about 40 mg of famotidine.

16. A method for treating and preventing osteoarthritis in patients susceptible to developing NSAID induced gastric and duodenal ulcers comprising administering a therapeutically effective amount of a composition comprising:

(a) a matrix containing core having a therapeutically effective amount of a first drug;

(b) a sustained release layer covering said matrix containing core and having a first portion of a second drug; and

(c) an immediate release layer covering said sustained release layer and having a second portion of said second drug,

wherein said sustained and said immediate release layer together provide a therapeutically effective amount of said second drug.

17. A method as defined in claim 16, wherein said matrix containing core further comprises insoluble polymers and adjuvants.

18. A method as defined in claim 17, wherein said insoluble polymers are selected from the group consisting of cellulosic materials, polyvinyl acetates, polyvinyl alcohols, methacrylates, and non-crosslinked polyvinylpyrolidone.

19. A method as defined in claim 17, wherein said adjuvants are selected from the group consisting of sucrose, lactose, colloidal silica, and magnesium stearate.

20. A method as defined in claim 16, wherein said sustained release layer further comprises water-soluble and/or gel forming polymeric materials.

21. A method as defined in claim 16, wherein said immediate release layer further comprises pharmaceutically acceptable excipients selected from the group consisting of cellulose derivatives, sugar, soluble salts, colorants, fillers, anti-tacking agents and anti-static agents.

22. A method as defined in claim 20, wherein said sustained release layer comprises from about 75 to about 95% of said second drug.

23. A method as defined in claim 21, wherein said immediate release layer comprises from about 5 to about 25% of said second drug.

24. A method as defined in claim 16, wherein said first drug is an NSAID.

25. A method as defined in claim 24, wherein said NSAID comprises diclofenac.

26. A method as defined in claim 25, comprising from about 50 to about 150 mg of diclofenac, more preferably about 75 mg of diclofenac.

27. A method as defined in claim 16, wherein said second drug is an H_2-receptor antagonist.

28. A method as defined in claim 27, wherein said H_2-receptor antagonist is famotidine.

29. A method as defined in claim 28, comprising from about 20 to about 60 mg of famotidine, more preferably about 40 mg of famotidine.

30. A pharmaceutical tablet composition comprising:

(a) a matrix containing core comprising from about 50 to about 150 mg of diclofenac, more preferably 75 mg of diclofenac;

(b) a sustained release layer covering said matrix containing core, comprising from about 10 to about 40 mg of famotidine, preferably 30 mg of famotidine; and

(c) an immediate release layer covering said sustained release layer, comprising from about 5 to about 20 mg of famotidine, preferably about 10 mg of famotidine.

31. A multi-layer tablet comprising:

(a) a core comprising a mixture of excipients and a therapeutically effective amount of a first drug, wherein said core allows for the sustained release of said first drug;

(b) a first layer covering said core, comprising water-soluble and/or gel forming polymeric materials in which is dispersed a first portion of a second drug, said first layer allowing for the sustained release of said first portion; and

(c) a second layer covering said first layer comprising a mixture of excipients and a second portion of said second drug, said second layer allowing for the immediate release of said second portion.

ABSTRACT

A pharmaceutical composition comprising a matrix containing core having a pharmaceutically effective amount of a first drug; a second layer covering the matrix containing core layer and having a first portion of a second drug and/or an additional portion of the first drug; and a third or more layers containing a second portion of the second drug and/or additional drugs.

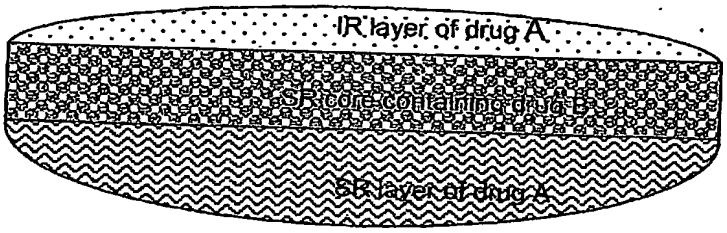

Figure 1

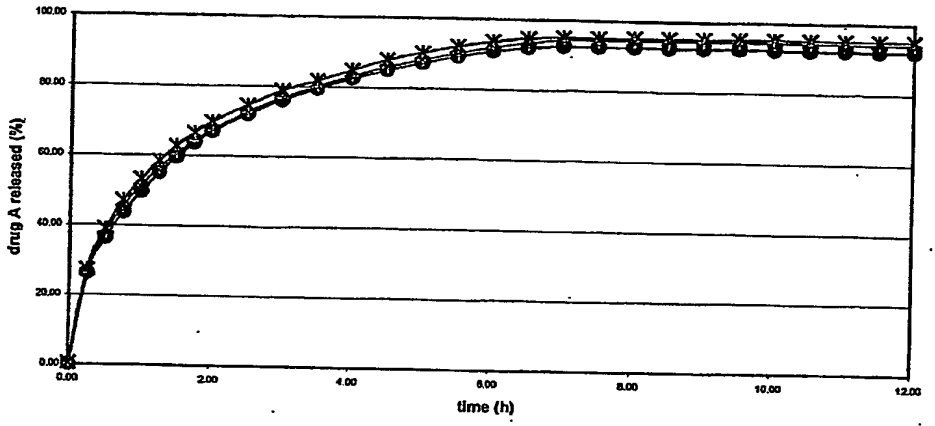
100.00
80.00
60.00
40.00
20.00
0.00
drug A released (%)
0.00
2.00
4.00
6.00
8.00
10.00
12.00
time (h)

Figure 2

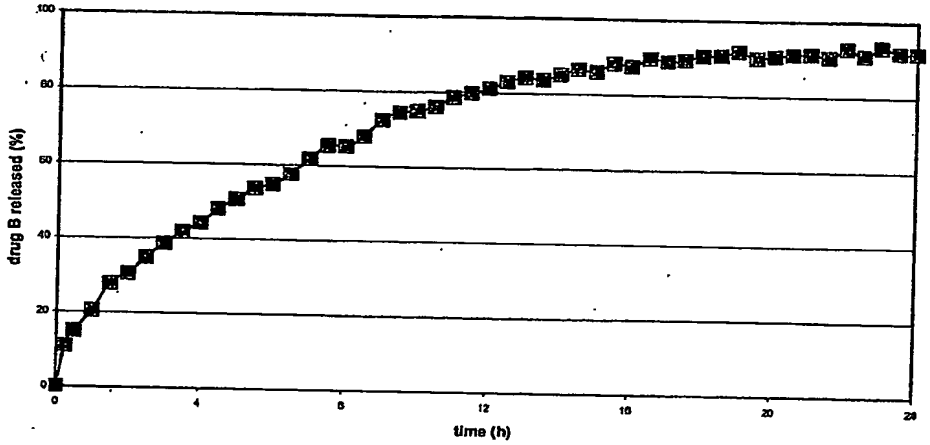

Figure 3

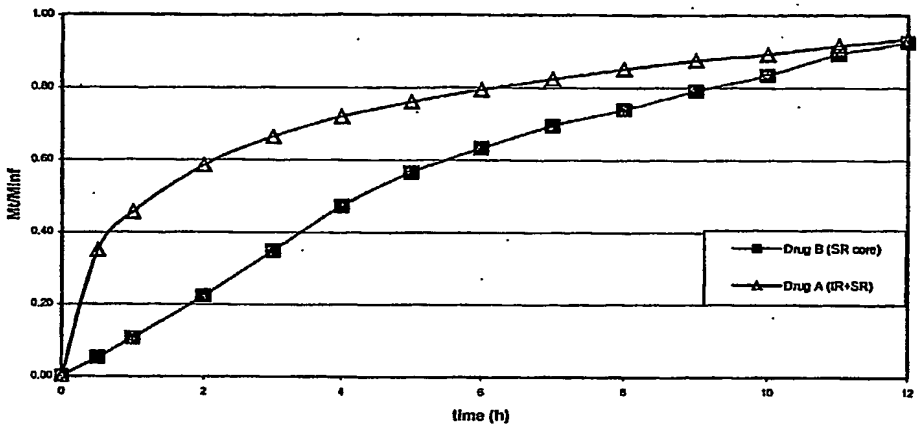
1.00
0.80
0.60
0.40
0.20
0.00
Mt/Minf
0
2
4
6
8
10
12
time (h)
Drug B (SR core)
Drug A (IR+SR)

Figure 4